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(54) CRYOGENIC APPARATUS

KRYOGENE VORRICHTUNG

APPAREIL CRYOGENIQUE

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- PATENT ABSTRACTS OF JAPAN vol. 010 no. 308 (P-508) ,21 October 1986 & JP-A-61 122542 (CHIYODA SEISAKUSHO:KK) 10 June 1986,

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Description

This invention relates to novel devices and methods for freezing drops of liquid reagent. In particular, it relates to devices and methods for freezing liquid reagents useful in the analysis of biological samples.

In preparing reagents for convenient and efficient testing of clinical biological samples, it is frequently important to obtain dry chemical blends in uniform, discrete amounts. These reagents must be efficiently and economically prepared in small precisely measured quantities. Reagents comprising organic materials, however, tend to spoil or degrade on storage, thus creating quality control problems. Thus, reagents are typically provided in dried form to increase stability. This is preferably done by freezing and lyophilizing the aqueous solutions comprising the reagents to form reagent spheres.

US-A-4 848 084 relates to a method and apparatus for the generation of frozen droplets. Liquid is fed under pressure through a nozzle which provides a continuous stream of liquid which breaks apart to form droplets. The cryogenic liquid in the freezing tank is agitated with an agitator. US-A-4 982 577 discloses an apparatus and method for freezing droplets of liquid product. The apparatus uses cryogenic liquid, which flows along a ramp or sluiceway to freeze the droplets. US-A-4 989 416 discloses an elongate tunnel which is inclined to the horizontal and which can be rotated along its longitudinal axis. Rotation of the tunnel carries the particles out of the liquid nitrogen contained therein. US-A-4 798 614 relates to a freezing apparatus using a rotary chamber which rotates about a horizontal axis. US-A-4 760 712 discloses a rotary chilling plate on which articles to be frozen are placed in brine. US-A-4 920 762 discloses a method and apparatus for producing cryogenic targets using a mold assembly. US-A-4 870 829 discloses a biological freezing apparatus containing a specimen holder which is lowered into a tank comprising a cryogenic liquid. US-A-4 595 226 relates to a gas sample collection device which includes a specular carousel having at least one reflective surface for holding a sample deposited thereon.

US-A-4 256 576 relates to a process for the creation of crystal aggregates in one part of the tank by heat transfer from a fluid disposed in another part of the tank. Both parts are separated from each other by a flexible membrane. US-A-3 282 064 relates to cryogenic or refrigerant regeneration for use in closed cycle systems. US-A-2 845 472 relates to an apparatus for cooling a transformer and means for recirculating the liquid coolant during the operation of the apparatus. US-A-2 835 477 relates to an apparatus and method for controlling temperature in a bath. The temperature of the liquid bath is controlled by means of a temperature control conduit immersed in the bath through which the cooling liquid is circulated. US-A-2 21 [illegible]19 relates to an apparatus and method for cooling bottled beverages in which the cooling liquid is recirculated through a recirculation loop.

JP-A-61 122542 shows a cryogenic apparatus used for freezing samples, comprising a means for dispensing a sample and below that means, a refrigerant tank filled with a cryogenic liquid. A disk-shaped circular rotatable carousel is arranged in the cryogenic liquid. The carousel is provided with multiple holes for receiving flanged metallic hollow blocks, which are immersed in the cryogenic liquid to fill therewith and held below the surface of the cryogenic liquid. The carousel is rotated by rotating means.

US-A-4 323 478 shows an apparatus, comprising a vessel and a dispensing means that feeds high amounts of drops into the vessel which is filled with cryogenic liquid, wherein the vessel is rotated by means of a motor.

The invention relates to methods and devices for freezing drops of liquid reagent solutions in a cryogenic liquid. The apparatus of the present invention comprises means for dispensing uniform, precisely measured drops of a liquid reagent and a rotatable carousel positioned below the dispensing means. The upper surface of the carousel has a plurality of trays each containing a cryogenic liquid, typically liquid nitrogen, for receiving the drops of liquid reagent. Each tray preferably comprises a plurality of removable separators to facilitate the removal of the frozen drops. The separators and trays are preferably designed to be used directly in a lyophilizer.

The apparatus also contains means for rotating the carousel about its vertical axis. The apparatus preferably comprises means for coordinating the rotation of the carousel with the dispensing of the drops, typically a photosensor.

The dispensing means preferably comprises a nozzle tip, through which the liquid is dispensed, a cowling around the nozzle tip and a gas port for blowing gas [illegible] the nozzle tip thereby preventing moisture condensation on the nozzle tip.

The liquid reagent solution preferably comprises a reagent useful for the analysis of a biological sample, such as blood. To ensure that the resulting lyophilized reagent spheres are uniform in size, the apparatus of the invention preferably includes means for degassing the liquid reagent solution before dispensing.

It is the object of the present invention to provide an improved technique (device and method) for forming reagent spheres allowing to work with better quality results, and to provide the improved reagent sphere thereof.

This object is achieved with the features of apparatus claim 1, method claim 13 and product claim 19, respectively.

Features, details, advantages and potentials of the techniques and products of present invention will become more appearant in the following description in conection with the drawings, wherein

Fig. 1 is a perspective view of an embodiment of the present invention; and

Fig. 2 is a top plan view of the carousel from Fig. 1.

The present invention provides devices and methods for producing lyophilized reagent spheres useful in analyzing biological samples, such as blood plasma or serum, in centrifugal analyzers. The reagent spheres are prepared from reagents suitable for any of a number of analytical assays of biological samples.

The lyophilized reagent spheres produced by the devices and methods of the present invention are suitable for use in centrifugal analyzers for optically analyzing biological fluids, in particular blood plasma or serum. Centrifugal rotors used in such analyzers typically co[illegible]prise means for mixing the blood with an appropriate diluent and separating plasma from cellular material. The rotor[illegible] p[illegible]ovide for distribution of the diluted plasma into a plurality of cuvettes within the rotor so that different optical an[illegible] procedures may be performed without having to transfer aliquots of the fluid from the apparatus. One or more r[illegible] spheres comprising the reagents necessary for a desired assay are provided in each cuvette.

The rotors and methods described in the following documents are preferably used: US-A-5 061 381, US-A-5 173 193, US-A-5 122 284, and US-A-5 18 344. The entire disclosure of these applications are incorporated herein by reference The above applications disclose centrifugal rotors for separating plasma from whole blood that include a plurality of internal chambers and passages for combining blood plasma or serum with one or more reagents and distributing the plasma or serum to a plurality of individual test wells. The chambers and passages necessary for separating the whole blood into plasma are located radially outward from metering chambers that deliver precisely measured volumes of blood and/or diluent to a separation chamber. The separation chamber includes a radially-outward cell trap. Spinning of the rotor causes the cellular components of the whole blood to be sequestered in the cell trap. The separated plasma is then delivered to a plurality of test wells or cuvettes. The above separation and aliquoting steps typically occur as a result of centrifugal force generated by the spinning rotor.

The compositions in combination with the rotors described above are particularly suitable for analyzing blood plasma or diluted blood plasma. They are also useful with a wide variety of other biological fluids, such as urine, sputum, semen, saliva, ocular lens fluid, cerebral fluid, spinal fluid, amniotic fluid, and tissue culture media, as well as food and industrial chemicals, and the like.

The compositions are particularly suitable for per[illegible]ming a wide variety of analytic procedures which are beneficially or necessarily performed on blood plasma [illegible]r diluted [illegible]lasma. The analytic procedures will generally require that the blood plasma be combined with one or more reagents so that some optically detectable change occurs in the plasma which may be related to measurement of a particular component or characteristic of the plasma. Preferably, the plasma will undergo a reaction or other change which results in a change in color, fluorescence, luminescence, or the like, which may be measured by conventional spectrophotometers, fluorometers, light detectors, etc. In some cases, immunoassays and other specific binding assays may be performed in the test wells. Generally, however, such assay procedures must be homogeneous and do not require a separation step. In other cases, it will be possible to accommodate heterogeneous assay systems by providing a means to separate blood plasma from the test wells after an immunological reaction step has occurred.

Conventional blood assays which may be performed include glucose, lactate dehydrogenase, serum glutamicoxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), blood urea (nitrogen) (BUN), total protein, alkalinity, alkaline phosphatase, c-reactive protein bilirubin, calcium, chloride, sodium, potassium, magnesium, and the like. This list is not exhaustive and is intended merely as being exemplary of the assays which may be performed using the apparatus and method of the present invention. Usually, these tests will require that the blood plasma be combined with one or more reagents which result in a visually detectable, usually photometrically detectable, change in the plasma. Suitable reagent solutions a[illegible] disclosed in US-A-5 413 732, which is incorporated herein by reference.

The lyophilized reagent spheres of the [illegible]ent invention dissolve quickly in an aqueous sample solution, or diluent. A sample solution of the present invention n[illegible] a diluted or undiluted biological sample. The reagent spheres typically dissolve in less than about 30 seconds, p[illegible]ly less than about 10 seconds. The rapidity of dissolution gives the impression that the reagent sphere "explo[illegible]" and distributes the dissolving chemicals throughout the reconstituting volume. Rapid dissolution of the spheres is facilitated by a chemical lattice structure which quickly conducts water into the reagent sphere. To form the chemical lattice, fillers are included in the aqueous solution used to produce the spheres. As the reagent spheres are lyophilized, these molecules facilitate formation of a network of open spaces or a chemical lattice in the spheres. The filler components of the reagent spheres are typically polymeric compounds, such as bovine serum albumin, polyethylene glycol, dextran, Ficoll® (Pharmacia LKB Biotechnology, Inc., Piscataway, New Jersey), or polyvinylpyrrolidone. In addition, emulsifiers such as sodium cholate and the like are useful as fillers. Monosaccharides and their derivatives, such as mannitol or the polyalcohol, myo-inositol, can also be used. Depending upon the assay, the fillers can be used individually or in combination with one or more of the other filler components.

In addition to fillers, the reagent spheres of the present invention also comprise one or more surfactants at concentrations sufficient to inhibit bubble formation when the spheres are rapidly rehydrated. As described above, bubbles are detrimental to the assays because they interfere with optical measurements. If the reagent spheres comprise

surfactants at the appropriate concentrations, however, such problems are avoided. Suitable surfactants include non-ionic detergents such as polyoxyethylene 9 lauryl ether, octoxynol 9, Synthrapol®, NP-90, Trycol® 5941, Trycol® 6735 and the like. Ionic detergents such as Gafac® 560, sodium dodecyl sulfate and the like are also suitable. Typically, the surfactants are present in the reconstituted reagent spheres at a concentration between about 0.08g and about 3.1g per 100ml. The surfactant concentration used will depend upon the particular reagents used in the assay.

The fillers and surfactants used in a p[illegible]ticular reagent sphere preparation are preferably selected so as to minimize interference with the assay. In addition, [illegible]vide reagent spheres of the correct size in a test well, the components are typically concentrated in the reagent s[illegible] Upon rehydration with a predetermined volume of sample, the reagents and other components are present in the [illegible] concentration. For instance, the components of the reagent spheres for alkaline phosphate determinations a[illegible]pically at about 6x concentration and total protein reagents are at about 2.7x concentration. The ideal concentration for the reagents for particular assay can be easily determined, depending upon size of the test well, sample volume, and the like.

The reagent spheres produced by the apparatus of the present invention are prepared from reagents suitable for any of the analytical assays discussed above. Typically, an aqueous solution comprising the reagents is prepared. To ensure uniform composition of the reagent spheres, the solution must be homogeneous and all constituents must be fully dissolved or in suspension. The devices of the present invention are then used to dispense individual drops of the solution into a carousel comprising cryogenic liquid, preferably liquid nitrogen. A cryogenic liquid as used herein refers to a liquified gas having a normal boiling point below about -75° C, preferably below about -150° C.

The frozen masses are then removed from the cryogenic liquid and lyophilized to produce the reagent spheres. The reagent spheres typically comprise less than about 6% residual moisture, preferably less than about 3%. Lyophilization is carried out according to standard procedures known in the art. Typically, the frozen drops are lyophilized for about 4 hours to about 24 hours at 6,6 Pa to 59,2 Pa (about 50 to about 450 mTorr), preferably, about 6 hours at about 26,3 Pa (200 mTorr).

The drops are uniform and precisel[illegible]sured so that the resulting dried reagent spheres have uniform mass. The uniformity of the reagent spheres ob[illegible] the need for an additional tableting step to obtain uniform size. When the drops are uniform and precisely mea[illegible] the imprecision of the mass (coefficient of weight variation) of the reagent spheres prepared from the drops is [illegible]an about 3%, and preferably between about 0.3% and about 2.5%. To further decrease the coefficient of weight variation, the aqueous solution is preferably degassed using a vacuum pump or vacuum line before the drops of solution are dispensed.

To obtain values for coefficient of weight variation, known quantities of reagent spheres are weighed. The coefficient of variation (C.V.) is then determined as follows:

$$C.V. = J/\bar{x} \times 100$$

wherein

$$J = \text{standard deviation (for } n \text{ sphere)} = \left[\frac{(x-\bar{x})^2}{n-1}\right]^{1/2}$$

x = weight of one sphere

$\bar{x}$ = mean (for "n" sphere) = $\Sigma x/n$

The device of the present invention comprises dispensing means which provide the precision necessary to produce uniform drops. A high precision pump is used to pump the liquid through the dispensing means. The pump should be of a design which minimizes shear and heat generation in the pump head. Typically, an IVEK model AAA pump (N. Springfield, VT) is used to pump the liquid reagent solution through the dispensing means. The pump system should also be of a design to allow control of the pump rate, dispensing volume, fluid drawback in the line and dispensing frequency. The term "pump rate" applies to the speed with which the pump motor opens and closes the pump cavity. The term "drawback" refers to the distance the fluid meniscus at the outlet of the dispensing means, moves back during the pump cycle. The drops are typically dispensed with a frequency ranging from 1 to 3 drops per second and usually dispensed with a frequency of 1 to 2 drops per second. There is no lower limit to dispensing frequency.

For instance, in preparing reagent spheres for total protein determinations, 2.96 µl drops are typically used, for C-reactive protein and alkaline phosphatase determinations, 2.67 µl are used. Volumes appropriate for other tests are as follows: SGOT, 4.0 µl; potassium, 4.0 µl; creatinine, 4.0 µl; bilirubin, 2.667 µl; amylase, 2.667 µl; cholesterol, 2.667

µl; uric acid, 3.478 µl; and glucose, 2.065 µl.

The dispensing means of the present invention preferably comprises a nozzle tip designed to provide substantially uniform drop size. A variety of nozzle tips can be used so long as sufficient uniformity of drop size is provided. The nozzle tips are typically made of Trifluoroethylene or some other polymer with equivalent rigidity and surface characteristics. The size of the orifice in the nozzle tip will depend upon the composition of the liquid reagent and the operating pressure used to pump the reagent. Typically the inside diameter of the orifice in the nozzle tip is between 0.51 and 1.02 mm (0.020 and 0.040 inches), usually between about 0.686 and 0.889 mm (0.027 and 0.035 inches), and preferably between about 0.737 and 0.787 mm (0.029 and 0.031 inches). The nozzle tip is typically tapered and has a tip wall thickness ranging from 0.127 mm (0.005 inches) to 0.406 mm (0.016 inches) depending upon the properties of the liquid reagent being dispensed.

The dispensing means is preferably positioned a sufficient distance above the cryogenic liquid surface to permit the fluid drop to form a sphere before it lands on the surface of the cryogenic liquid. However, spacing the dispensing means too great a distance above the cryogenic liquid permits the drop to break up into droplets prior to contacting the cryogenic liquid. The dispensing means is typically positioned between about 8 cm and 13 cm above the cryogenic liquid, preferably about 10 cm. The precise distance used will depend upon the particular design of the apparatus and the design of the dispensing means used. This distance can be determined by minimal experimentation once other design variables are specified. Alternately, the dispensing means may be oriented such that the reagent drops follow a trajectory which allows them to impact the surface of the cryogenic liquid with a velocity near zero cm/sec. This typically will require the dispensing means to be oriented 0°-180° to the cryogenic liquid surface.

In the present invention, the cryogenic liquid is contained within trays placed on a rotatable carousel. Each tray is preferably divided into subsections using removable separators. The carousel rotates about its vertical axis so that each tray is successively rotated under the dispensing means. The drops are separated by the removable separators after dispensing. This provides each bead with the same exposure time to the cryogenic liquid (dwell time) and ensures that the beads will have completely frozen and sunk below the surface of the liquid before dispensing the next drop of reagent into the same area. This prevents the formation of double beads, i.e. beads which have stuck together during freezing. The velocity of the rotating carousel is selected such that no movement to the cryogenic liquid is imparted, thereby maintaining the smooth surface for dispensing.

Referring now to Figures 1 and 2, a cryogenic apparatus 2 constructed in accordance with the principles of the present invention will be described in detail A liquid reagent solution 4 is held in reservoir 6 where it is kept at an appropriate temperature via recirculating water bath 8 and jacket 10. The temperature of the water in the jacket ranges from room temperature to 4°C depending upon the reagent properties. The temperature of the reagent liquid effects the viscosity of the reagent liquid which in turn effects the overall dispensing precision. The liquid reagent is drawn through line 12 by the dispensing pump 14 and delivered to the degassing chamber 16. The solution is degassed for about 29 minutes using vacuum pump 18. The solution is then drawn through line 20 to the dispensing means 22.

The dispensing means 22 comprises nozzle tip 24 surrounded by cowling 26. A dry nitrogen dispensing tip 28 supplies dry nitrogen from dry nitrogen tubing 30 and creates a microenvironment around the nozzle tip which prevents moisture from condensing and the tip from freezing. The dry nitrogen gas also creates a positive pressure which preferentially redirects any cryogenic liquid vapor away from the nozzle tip and towards an exhaust port 32. The dry nitrogen is typically supplied at a pressure of between 703 and 1055 hPa (10 and 15 pounds per square inch-psi).

Liquid reagent 4 dispensed from the dispensing means 22 is received by the cryogenic liquid 34 contained in a carousel 36 positioned below the dispensing mean 22. The carousel 36 is rotatably mounted in the insulated tank 38 and is rotated about carousel spindle 40 positioned at the vertical axis of rotation of the carousel 36. The spindle 40 is connected to a motor 42 which drives the rotation of the carousel. The carousel is usually rotated at between about 4 and 10 rpm. The preferred range is between about 4 and 6 rpm.

The carousel spindle 40 comprises a photosensor trigger 44 which is detected by photosensor 46 to allow coordination of the rotation of the spindle with the rate of dispensing of drops of liquid reagent by the dispensing means 22. Specifically, the trigger 44 has a number of pegs (not shown) projecting radially from its outer edge which act as optical triggers for the photosensor 46. The photosensor 46 is a standard photosensor well known to those skilled in the art. It typically includes a reflective photo-emitter detector module which furnishes a light source and a phototransistor to determine if light has been reflected off of a predetermined surface. A conditioning circuit is used to bias the electro-optical module to control length of time for the dispense pump. A driver is used to control a relay which isolates the control circuit from the dispensing mechanism.

Cryogenic liquid (typically liquid nitrogen) is supplied through supply line 48 and is dispensed through cryogenic liquid dispensing means 50. This dispensing means includes a protective cowling 52. The insulated tank 38 is supported by tank support frame 54 and the motor 42 is positioned on the motor support shelf 56.

The carousel of the present invention is seen more clearly in Figure 2. The carousel is shown here as a circular disc. It will be understood, however, that other shapes (e.g., rectangular) may also be used. The carousel 36 comprises four dispensing trays 58, which each comprise a tab 60 to facilitate removal of the trays 58 from the carousel 36. Each

tray 58 is subdivided by separators 62 which also comprise separator tabs 64 to facilitate removal of the separators 62 from the trays 58. The rate of dispensing of liquid reagent is a function of the size of the trays 58 in the carousel, the rate of rotation and the number of separators 62. These parameters are adjusted to ensure the appropriate dwell time of the bead before sinking below the 'ace of the cryogenic liquid. After each tray 58 receives the desired number of liquid drops, it is removed and replac ith another tray. After completion of dispensing, the trays 58 and their separators 62 are removed and put direc.., nto the lyophilizer.

Although the foregoing embodiment has been described in detail for purposes of clarity of understanding, it will be obvious that certain modifications may be practiced within the scope of the claims.

Claims

1. A cryogenic apparatus using an amount of a cryogenic liquid for freezing liquid reagent to spheres, said apparatus comprising

   - means (22) for dispensing uniform, precisely measured drops of a liquid reagent (4);
   - a rotatable carousel (36) having a vertical axis of rotation;
   - a plurality of trays (58) disposed on an upper surface of the carousel (36) being positioned to receive reagent drops from the dispensing means (22);
   - means (40, 42, 44, 46) for rotating the carousel (36) about the vertical axis,

   characterized in that each tray (58) is ac..pted to receive solely the amount of cryogenic liquid (34) for freezing a single drop of liquid reagent (4).

2. Apparatus according to claim 1, wherein each tray (56) comprises a plurality of removable separators (62).

3. Apparatus according to claim 1 or 2, wherein the cryogenic liquid (34) is liquid nitrogen.

4. Apparatus according to one of claims 1 to 3, wherein the liquid reagent (4) comprises a reagent useful for the analysis of blood.

5. Apparatus according to one of claims 1 to 4, further comprising means (16, 18) for degassing the liquid reagent (4).

6. Apparatus according to one of claims 1 to 5, wherein the carousel (36) is disposed within an insulated tank (38).

7. Apparatus according to one of claims 1 to 6, wherein the means (22) for dispensing comprises a nozzle tip (24) through which the liquid is dispensed, a cowling (26) around the nozzle tip (24) and a gas port (28) for blowing gas along the nozzle tip (24) thereby preventing moisture condensation on the nozzle tip (24).

8. Apparatus according to claim 7, where he gas is nitrogen.

9. Apparatus according to one of claims 1 to 8, wherein the carousel (36) rotates at a speed selected such that the cryogenic liquid (34) has a smooth surface.

10. Apparatus according to one of claims 1 to 9, further comprising means (44, 46) for coordinating the rotation of the carousel (36) with the dispensing of drops of liquid reagent (4).

11. Apparatus according to claim 10, wherein the means (44, 46) for coordinating the rotation of the carousel (36) comprises a photo sensor (46).

12. Apparatus according to one of claims 1 to 11, wherein the trays (58) are designed to be used in a lyophilizer.

13. Method for forming reagent spheres comprising the steps of

   - disposing at least one tray (58) on the upper surface of a carousel (36) rotatable around a vertical rotation axis;
   - dispensing a uniform, precisely measured drop of a liquid reagent (4) into the tray (58) containing at least one entity of cryogenic liquid (34), whereby e drop is frozen;
   - separating the frozen drops from the cryogenic liquid; and

- lyophilizing the frozen drops, thereby forming the reagent spheres

characterized in

that the entities of cryogenic liquid (34) are separated from each other to avoid passage of a drop; and that after each dispensing step, the carousel (36) is submitted to a rotation step to avoid that a second drop is dispensed into the same entity of cryogenic liquid (34) that received the previous drop.

14. Method according to claim 13. wherein the frozen drops remain in the tray (58) during the separating step, and the lyophilizing of the frozen drops is effected in the tray (58).

15. Method according to claim 13 or 14, wherein the liquid reagent (4) comprises a reagent useful for the analysis of blood.

16. Method according to one of claims 13 to 15, wherein the liquid reagent (4) is degassed before dispensing.

17. Method according to one of claims 13 to 16, wherein the cryogenic liquid (34) is liquid nitrogen.

18. Method according to one of claims 13 to 17, wherein the rotation step is generated by a trigger means (44, 46) coupled to a motor for driving the ca sel (36).

19. A reagent sphere produced accordin the method of one of claims 13 to 18.

Patentansprüche

1. Kryogene Vorrichtung, die eine Quantität an kryogener Flüssigkeit für das Frieren von flüssigem Reagens zu Kugeln verwendet, welche Vorrichtung umfaßt:

- Mittel (22) für das Austragen gleichförmiger, präzise bemessener Tropfen eines flüssigen Reagens (4),
- einen Drehtisch (36) mit einer vertikalen Drehachse,
- eine Mehrzahl von Trögen (58), die auf einer Oberseite des Drehtisches (36) positioniert sind, um Reagenstropfen von den Austragmitteln (22) zu empfangen,
- Mittel (40, 42, 44, 46) für das Verdrehen des Karussells (36) um die Vertikalachse,

dadurch gekennzeichnet, daß jeder Trog (58) für die Aufnahme nur der Menge an kryogener Flüssigkeit (34) für das Frieren eines einzelnen T ens des flüssigen Reagens (4) ausgebildet ist.

2. Vorrichtung nach Anspruch 1, bei der je Trog (58) eine Mehrzahl von entnehmbaren Separatoren (62) umfaßt.

3. Vorrichtung nach Anspruch 1 oder 2, bei der die kryogene Flüssigkeit (34) flüssiger Stickstoff ist.

4. Vorrichtung nach einem der Ansprüche 1 bis 3, bei der das flüssige Reagens (4) ein für die Blutanalyse geeignetes Reagens umfaßt.

5. Vorrichtung nach einem der Ansprüche 1 bis 4, ferner umfassend Mittel (16, 18) für die Entgasung des flüssigen Reagens (4).

6. Vorrichtung nach einem der Ansprüche 1 bis 5, bei der der Drehtisch (36) innerhalb eines isolierten Tanks (38) angeordnet ist.

7. Vorrichtung nach einem der Ansprüche 1 bis 6, bei der die Mittel (22) für das Austragen eine Düsenspitze (24) umfassen, durch die die Flüssigkeit ausgetragen wird, einen ringsum die Düsenspitze (24) angeordneten Mantel (26) und einen Gasauslaß (28) für das Blasen von Gas längs der Düsenspitze (24), wodurch Flüssigkeitskondensation an der Düsenspitze (24) verhindert w d.

8. Vorrichtung nach Anspruch 7, bei der das G s Stickstoff ist.

9. Vorrichtung nach einem der Anspr[illegible] bis 8, bei der der Drehtisch (36) mit einer Drehzahl umläuft, die so ausgewählt ist, daß die kryogene Fl[illegible]sigkeit (34) eine glatte Oberfläche aufweist.

10. Vorrichtung nach einem der Ansprüche 1 bis 9, ferner umfassend Mittel (44, 46) für das Koordinieren der Drehung des Drehtisches (36) mit dem Austrag von Tropfen des flüssigen Reagens (4).

11. Vorrichtung nach Anspruch 10, bei der die Mittel (44, 46) für das Koordinieren der Drehung des Drehtisches (36) einen Fotosensor (46) umfassen.

12. Vorrichtung nach einem der Ansprüche 1 bis 11, bei der die Tröge (58) für die Verwendung in einem Gefriertrockner konstruiert sind.

13. Verfahren für die Bildung von Reagenskugeln, umfassend die Schritte:

- Anordnen mindestens eines Troges (58) auf der Oberseite eines Drehtisches (36), der um eine vertikale Drehachse verdrehbar ist,
- Austragen eines gleichförmigen, [illegible] bemessenen Tropfens eines flüssigen Reagens (4) in den Trog (58), der mindestens eine Einheit von [illegible]gener Flüssigkeit (34) enthält, wodurch der Tropfen gefroren wird,
- Trennen des gefrorenen Tropfen[illegible] der kryogenen Flüssigkeit, und
- Gefriertrocknen des gefrorenen T[illegible]opfens, wodurch Reagenskugeln gebildet werden,

dadurch gekennzeichnet, daß die Ei[illegible]heiten von kryogener Flüssigkeit (34) voneinander getrennt sind, um die Passage eines Tropfens zu vermeiden und daß nach jedem Austragschritt der Drehtisch (36) einem Drehschritt unterworfen wird, um zu vermeiden, daß ein zweiter Tropfen in dieselbe Einheit von kryogener Flüssigkeit (34) eingesetzt wird, die den vorhergehenden Tropfen empfangen hat.

14. Verfahren nach Anspruch 13, bei dem die gefrorenen Tropfen in dem Trog (58) während des Abtrennschritts verbleiben und das Gefriertrocknen der gefrorenen Tropfen in dem Trog (58) ausgeführt wird.

15. Verfahren nach einem der Ansprüche 13 oder 14, bei dem das flüssige Reagens (4) ein für die Blutanalyse geeignetes Reagens umfaßt.

16. Verfahren nach einem der Ansprüche 13 bis 15, bei dem das flüssige Reagens (4) vor dem Austrag entgast wird.

17. Verfahren nach einem der Ansprüche [illegible] bis 16, bei dem die kryogene Flüssigkeit (34) flüssiger Stickstoff ist.

18. Verfahren nach einem der Ansprüche 1[illegible] bis 17, bei dem der Drehschritt durch ein Triggermittel (44, 46) erzeugt wird, das mit einem Motor für den An[illegible]ieb des Drehtischs (36) gekoppelt ist.

19. Eine Reagenskugel, hergestellt gemäß dem Verfahren nach einem der Ansprüche 13 bis 18.

Revendications

1. Appareil cryogénique utilisant une quantité d'un liquide cryogénique pour congeler un réactif liquide sous forme de sphères, ledit appareil comprenant

- des moyens (22) pour distribuer des gouttes uniformes, mesurées de façon précise, d'un réactif liquide (4);
- un carrousel (36) rotatif ayant un axe de rotation vertical;
- une pluralité de plateaux (58), disposés sur une surface supérieure du carrousel (36), étant positionnés pour recevoir des gouttes de réactif provenant des moyens de distribution (22);
- des moyens (40, 42, 44, 46) pour e[illegible]ner en rotation le carrousel (36) autour de l'axe vertical, caractérisé en ce que chaque plateau (58) est a[illegible]é pour recevoir seulement la quantité de liquide cryogénique (34) destinée à congeler une unique goutte de réactif liquide (4).

2. Appareil selon la revendication 1, dans lequel chaque plateau (58) comprend une pluralité de séparateurs (62) amovibles.

3. Appareil selon la revendication 1 ou 2, dans lequel le liquide cryogénique (34) est l'azote liquide.

4. Appareil selon l'une des revendications 1 à 3, dans lequel le réactif liquide (4) comprend un réactif utile pour l'analyse du sang.

5. Appareil selon l'une des revendications 1 à 4, comprenant en outre des moyens (16, 18) pour dégazer le réactif liquide (4).

6. Appareil selon l'une des revendications 1 à 5, dans lequel le carrousel (36) est disposé à l'intérieur d'un réservoir isolé (38).

7. Appareil selon l'une des revendications 1 à 6, dans lequel les moyens de distribution (22) comprennent une extrémité de buse (24), à travers laquelle le liquide est distribué, un tablier (26) autour de l'extrémité de buse (24) et un orifice à gaz (28) pour souffler du gaz le long de l'extrémité de buse (24) afin d'éviter une condensation d'humidité sur l'extrémité de buse (24).

8. Appareil selon la revendication 7, dans lequel le gaz est l'azote

9. Appareil selon l'une des revendications 1 à 8, dans lequel le carrousel (36) tourne à une vitesse sélectionnée pour que le liquide cryogénique (34) ait une surface lisse.

10. Appareil selon l'une des revendications 1 à 9, comprenant en outre des moyens (44, 46) pour coordonner la rotation du carrousel (36) avec la distribution des gouttes de réactif liquide (4).

11. Appareil selon la revendication 10, dans lequel les moyens (44, 46) pour coordonner la rotation du carrousel (36) comprennent un photodétecteur (46).

12. Appareil selon l'une des revendications 1 à 11, dans lequel les plateaux (58) sont conçus pour être utilisés dans un lyophiliseur.

13. Procédé pour former des sphères de réactif, comprenant des étapes de :

- disposer au moins un plateau (58) sur la surface supérieure d'un carrousel (36) pouvant tourner autour d'un axe de rotation vertical;
- distribuer une goutte uniforme, mesurée de façon précise, d'un réactif liquide (4) dans le plateau (58) contenant au moins une entité de liquide cryogénique (34), la goutte étant ainsi congelée;
- séparer les gouttes congelées du liquide cryogénique; et
- lyophiliser les gouttes congelées formant ainsi les sphères de réactif,

caractérisé en ce que les entités de liquide cryogénique (34) sont séparées les unes des autres pour éviter le passage d'une goutte;

- et en ce qu'après chaque étape de distribution, le carrousel (36) est soumis à une étape de rotation pour éviter qu'une deuxième goutte soit distribuée dans la même entité de liquide cryogénique (34) qui a reçu la goutte précédente.

14. Procédé selon la revendication 13, dans lequel les gouttes congelées restent dans le plateau (58) au cours de l'étape de séparation et dans lequel la lyophilisation des gouttes congelées est effectuée dans le plateau (58).

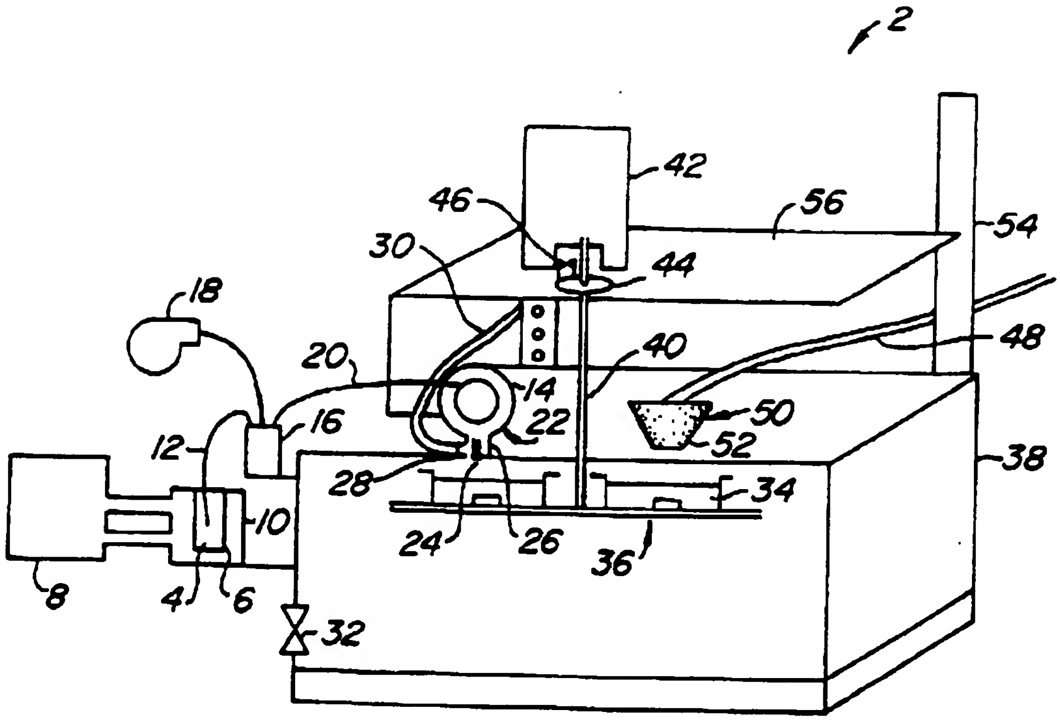
15. Procédé selon la revendication 13 ou 14, dans lequel le réactif liquide (4) comprend un réactif utile pour l'analyse du sang.

16. Procédé selon l'une des revendications 13 à 15, dans lequel le réactif liquide (4) est dégazé avant distribution.

17. Procédé selon l'une des revendications 13 à 16, dans lequel le liquide cryogénique est l'azote liquide.

18. Procédé selon l'une des revendications 13 à 17, dans lequel l'étape de rotation est engendrée par un moyen de déclenchement (34, 46) relié à un moteur pour entraîner le carrousel (36).

19. Sphère de réactif produite selon le procédé tel que défini par l'une des revendications 13 à 18.


2
42
46
56
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8
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6
32

FIG. 1.

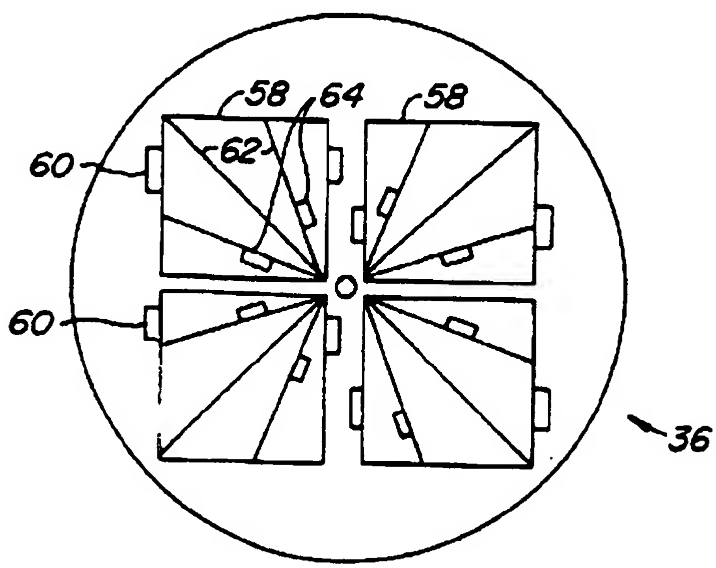
58
64
58
62
60
60
36

FIG. 2.